New Oral Therapies for Psoriasis

A Comprehensive Review

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ABSTRACT

Conventional oral therapies for psoriasis, including methotrexate, cyclosporine, and acitretin, have generally unfavorable safety profiles and are not ideal for long-standing use. Thus, new oral therapies are necessary for patients with more moderate disease, patients who prefer oral treatments to injectable biologics, and patients who failed conventional therapies. The authors review here the clinical and safety evidence of phosphodiesterase 4 inhibitor, apremilast, janus kinase inhibitors, including tofacitinib, and fumaric acid esters as additional options in oral psoriasis therapy.
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There is an unmet need for oral medications for treatment of psoriasis that can be administered long-term with favorable tolerability and safety. The authors review the currently available oral medications and the most promising new options.

CONVENTIONAL ORAL THERAPY

Oral therapies are used as monotherapy or adjunctive treatment in moderate-to-severe or recalcitrant psoriasis often before or after failure with topicals, phototherapy, or biologics. Methotrexate, cyclosporine, and acitretin have been the conventional mainstay oral therapies of psoriasis.

Methotrexate increases endogenous release of adenosine, an immune and anti-inflammatory modulator.[1] After 16 weeks of dose escalation from 7.5mg to 25mg weekly methotrexate, 35.5 percent of patients with plaque psoriasis achieved 75-percent reduction of psoriasis area and severity index (PASI75) compared to 79.6 percent on adalimumab 40mg bimonthly and 18.9 percent on placebo. Common adverse events (AEs) include infection, nasopharyngitis, and headache.[2] Serious AEs are teratogenicity, hepatotoxicity, renal failure myelosuppression, diarrhea and ulcerative stomatitis, pulmonary fibrosis, skin reactions, and opportunistic infection.[3]

Cyclosporine inhibits calcineurin phosphorylation, thereby preventing downstream interleukin (IL)-2 transcription, and is used short-term or intermittently for severe psoriasis flares, particularly pustular and erythrodermic psoriasis. Cyclosporine is advantageous for its rapid effect. Treatment occurs at 2.5 to 5.5mg/kg/day and from 12 to 24 weeks to limit cumulative nephrotoxicity.[4,5] In an eight-week trial comparing 3, 5, 7.5 mg/kg, and placebo, 36, 65, 85, and 0 percent, respectively, of patients reached clear or almost clear levels on physician's global assessment scale. Monitoring for hypertension, hyperlipidemia, hypomagnesemia, and hyperkalemia is necessary. Long-term treatment can cause chronic nephrotoxicity, hepatotoxicity, thrombotic microangiopathy, malignancies, neurotoxicity, and serious infection.[6]

Acitretin, a vitamin A-derived retinoid used in escalating doses from 10mg/day to 75mg/day, has historically been used to treat mild-to-moderate pustular, palmoplantar, and erythrodermic variant psoriasis. In a trial comparing 10, 25, and 50mg/day doses after eight weeks, 50, 40.5, and 53.8 percent of patients, respectively, reached PASI50.[8] Acitretin is useful in plaque psoriasis as combination therapy with phototherapy and biologics, but not as monotherapy given low remission rates (<50%).[7] Acitretin is non-immunosuppressive and AEs include dry eyes, lipid derangements, pancreatitis, hyperostosis, pseudotumor cerebri, hepatotoxicity, and teratogenicity.[9]

NEW ORAL THERAPY

Apremilast. *Mechanism of action.* Apremilast is a phosphodiesterase 4 (PDE4) inhibitor and decreases PDE4-mediated degradation of cyclic adenosine monophosphate, a secondary messenger that promotes

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PRACTICE POINTS
Conventional oral therapies including methotrexate, cyclosporine, and acitretin have a high risk of severe side effects and provide limited options for patients in need of long-term oral maintenance therapy.
New oral therapies in psoriasis are necessary for patients with psoriasis who failed or do not tolerate injectable biologics and conventional therapies.
A variety of novel small molecule inhibitors are in development, including janus kinase inhibitors and dimethylfumarate, and require further efficacy and safety investigation. Of these, apremilast, a phosphodiesterase inhibitor, is approved and has demonstrated a favorable safety profile in clinical trials.
Tofacitinib demonstrated promising efficacy in clinical investigation, but was declined FDA approval in late 2015. However, it is still under active investigation for psoriasis and other applications.

anti-inflammatory processes.[10]

Pharmacodynamics. Apremilast reduces epidermal thickness, K16 expression, and lymphocyte infiltration of target plaques.[11] Patients display significant changes in plasma levels of tumor necrosis factor (TNF)-alpha, IL-6, IL-8, IL-17, and IL-23.[12]

Pharmacokinetics. Apremilast has peak serum concentration at 1.5 hours and half-life of 7 hours. Metabolism is through cytochrome (CYP) 3A4 oxidation and other pathways, with urinary (58%) and fecal (39%) elimination. Most metabolites were at least 50-fold less active than apremilast.[11] Absolute bioavailability is 73 percent and volume of distribution (Vd) is 87 L.[13]

Efficacy. Apremilast was approved by the United States Food and Drug Administration (FDA) in March 2014 for psoriatic arthritis and in September 2014 for moderate-to-severe plaque psoriasis. In a Phase 2b randomized trial, 352 patients with moderate-to-severe psoriasis (body surface >10%) exhibited dose-dependent clinical response, with 29 percent (p<0.0001) of patients on 20mg BID and 41 percent (p<0.0001) of patients on 30mg BID apremilast reaching PASI75 at Week 16 compared to six percent of patients on placebo.[14] Two multicenter, Phase 3 trials—ESTEEM 1 and ESTEEM 2—compared apremilast 30mg BID and placebo after 16 weeks, and 33.1 percent versus 5.3 percent (p<0.0001) of patients, respectively, reached PASI75 in ESTEEM 1 and 28.8 percent versus 5.8 percent (p<0.0001) of patients, respectively, reached PASI75 in ESTEEM 2.[15,16] Forty-nine percent of patients included in ESTEEM 1 and more than 50 percent of patients included in ESTEEM 2 had severe psoriasis, defined as lesions in greater than 20 percent of body surface area. Notably, patients with nail, scalp, and palmoplantar involvement, also exhibited significant improvement. After 16 weeks, 44.6 percent (p<0.0001) of patients on apremilast saw a 50-percent reduction in nail psoriasis severity index compared to 18.7 percent in the placebo group. Likewise, 40.9 percent (p<0.0001) on apremilast improved in scalp physician global assessment from 3 or more (moderate to severe) to 0 to 1 (clear to minimal), compared to 17.2 percent on placebo. 65.4 percent (p<0.0315) on apremilast versus 31.3 percent on placebo improved in palmoplantar psoriasis physician's global assessment.[16]

Adverse effects and laboratory findings. Common AEs are nausea (17 vs. 7% placebo), diarrhea (17 vs. 6%), nasopharyngitis (9 vs. 6%), tension headache (8 vs. 4%), and headache (6 vs. 4%).[13] Onset occurs at the beginning of dosing and resolves within 1 to 2 weeks. There is no evidence of cardiovascular, renal, hepatic, or lymphoproliferative risk.[14,15] Depression and weight loss may occur. Use with P450 inducers is not recommended.[13]

Laboratory abnormalities occurred at similar rates between treatment and placebo groups, including triglyceridemia (12.5 vs. 8.3%), hypercholesterolemia (1.6 vs. 1.7%), lymphocytopenia (0.8 vs. 3.8%), and transaminitis (0 vs. 1.5%).[15]

Tofacitinib. *Mechanism of action.* Tofacitinib inhibits janus kinase (JAK) 1 and 3, which are involved in the JAK-STAT pathway of gene transcription. JAK3 interacts with JAK1 to activate cytokines and receptors involved in lymphocyte function. JAK inhibition suppresses receptors for numerous cytokines, including IL-15, which is highly expressed in psoriatic skin lesions and contributes to apoptotic-resistant keratinocytes.[17,18]

Pharmacodynamics. Patients show decreased lesional K16 expression, epidermal thickness, and lymphocytes in psoriatic plaques.[19]

Pharmacokinetics. Tofacitinib has rapid absorption with plasma concentration peaking in one hour, a half-life of 3.2 hours, and oral availability of 74 percent. Clearance is through cytochrome P450 oxidation, particularly CYP3A4. Metabolites have insignificant drug-related activity. Primary excretion occurs renally.[20]

Efficacy. A dose-ranging Phase 2b study showed

significant efficacy over placebo at 2mg (25 vs. 2%, $p<0.001$) by Week 12.[21] In the first of Phase 3 trials, PIVOTAL 1 and 2, 44 percent of patients on 5mg BID ($p<0.0001$) and 59.4 percent of patients on 10mg BID ($p<0.0001$) reached PASI75 endpoint at Week 16 compared to placebo (8.9%). Notably, patients at either dose also showed significant improvement in nail involvement.[22]

A 12-week Phase 3 noninferiority trial demonstrated comparable efficacy in reaching PASI75 between patients on 10mg BID tofacitinib (63.6%, $p<0.0001$) and 50mg BID etanercept (58.8%, $p<0.0001$) compared to placebo (5.6%). Notably, more patients on tofacitinib compared to etanercept reached PASI75 at Week 4 (19.4 vs. 8.1%, $p<0.0001$) and Week 8 (50.6 vs. 41.2%, $p<0.0144$), suggesting a quicker response time.[23]

Adverse events and laboratory findings. Common adverse effects occurred at higher rates in patients on tofacitinib 10mg BID than on placebo, and include nasopharyngitis (7.9% vs 5.6%), upper respiratory infection (5.5 vs. 3.1%), and headache (4.7 vs. 3.1%). Eight patients (1.1%) of the active groups in PIVOTAL 1 and four patients (0.5%) of the active groups in PIVOTAL 2 had viral reactivation of herpes zoster, with one case meeting serious infection criteria, compared to none in placebo groups.[22]

Several dose-dependent laboratory abnormalities occurred at higher rates in active groups comparing tofacitinib 5mg BID, 10mg BID, and placebo, including decreased hemoglobin (-0.3 vs. -0.4 vs. -0.1), decreased neutrophils (-0.21 vs. -0.37 vs. -0.02), lymphocytosis (+0.03 vs. +0.12 vs. +0.05), increased CPK (+41 vs. +65.5 vs. +7), increased LDL (+7.3% vs. +9.5% vs. 0%), and transaminitis (+1.9% vs. +3.2% vs. +1%).[22] Serious AEs, based on long-term safety data from rheumatoid arthritis trials, include infection, viral and tuberculosis reactivation, malignancy, lymphoproliferative disorders, nonmelanoma skin cancer, and gastrointestinal perforation.[24] Tofacitinib remains under active investigation, but was declined FDA approval in October 2015.

OTHER ORAL DRUGS

Jak inhibitors. ASP015K, a selective JAK3 inhibitor, recently completed a Phase 2a, randomized, dose-escalation trial. After six weeks of treatment, a significantly increased percentage of patients reached PASI50 on 10mg BID (63.2%, $p<0.05$), 25mg BID (47.6% $p<0.05$), 60mg BID (68.4%, $p<0.001$), 100mg BID (76.5%, $p<0.001$), and 50mg QD (47.4%, $p<0.05$) compared to placebo (17.2%).[25] Further investigations of safety, pharmacokinetics, and efficacy are ongoing.

Baricitinib (LY3009104), a JAK1/2 inhibitor, is still in early stages of investigation and recently completed a Phase 2b efficacy study (NCT01490632).

CF101. CF101, currently studied in rheumatoid arthritis and psoriasis, downregulates expression of A3 adenosine receptor (A_3AR), which is thought to propagate inflammatory and autoimmune states.[26] One dose-ranging Phase 2 trial of 1, 2, or 4mg BID demonstrated efficacy in the 2mg group only compared to placebo at Week 12 (35.5% vs. 16% at PASI50, $p<0.031$).[27] A Phase 2/3 trial (NCT01265667) is awaiting secondary endpoint results.

Oral fumaric acid esters. Oral fumaric acid esters, a combination of dimethylfumarate and other fumarate salts, have long been used for psoriasis in Europe and are currently approved in Germany as Fumaderm (Biogen Idec Inc.).

FP187 is an oral immunomodulator with the same dimethylfumarate formula as Fumaderm undergoing Phase 2 (NCT01230138) and 3 (NCT01815723) trials in the United States. Fumarates affects the psoriatic cell environment and inhibits T lymphocyte and dendritic cell survival.[28]

One meta-analysis demonstrates significant efficacy of oral fumaric acid esters over placebo to reach PASI50 (64% vs. 14%, $p<0.00001$) after 12 to 16 weeks of treatment and noninferiority to methotrexate. Common AEs are nausea, diarrhea, and facial flushing, which can occur in up to two out of three of patients.[29]

CONCLUSION AND FUTURE DIRECTIONS

There are promising new options of oral therapies in psoriasis for patients who have exhausted current treatments. Of these, only apremilast is approved. Apremilast has demonstrated efficacy and relative long-term safety. Patients should be warned of possible gastrointestinal distress, and dosages can be titrated accordingly. Tofacitinib is promising as it has demonstrated noninferiority to etanercept, although laboratory abnormalities, laboratory monitoring, and long-term safety are still in question. Other new oral therapies require further efficacy and safety investigation.

REFERENCES

1. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. *Arthritis Res.* 2002;4:266–273.
2. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol.* 2008;158:558–566.
3. Methotrexate [package insert]. Kent, UK: Pfizer Limited; 2002.
4. Ho VC, Griffiths CE, Albrecht G, et al. Intermittent short courses of cyclosporin (Neoral®) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group. *Br J Dermatol.* 1999;141:283–291.
5. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol.* 2010;63:925–946.
6. Neoral [package insert]. East Hanover, NJ: Novartis; 2015.
7. Dogra S, Yadav S. Acitretin in psoriasis: an evolving scenario. *Int J Dermatol*. 2014;53:525–538.
8. Gollnick H, Bauer R, Brindley C, et al. Acitretin versus etretinate in psoriasis. Clinical and pharmacokinetic results of a German multicenter study. *J Am Acad Dermatol.* 1988;19:458–468.
9. Soriatane [package insert]. Palo Alto, CA: Connetics Corporation; 2004.

10. Schafer PH, Parton A, Gandhi AK, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol.* 2010;159:842–855.
11. Gottlieb AB, Strober B, Krueger JG, et al. An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast. *Curr Med Res Opin.* 2008;24:1529–1538.
12. Schafer PH, Chen P, Fang L, et al. The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a Phase III, randomized, placebo-controlled trial (PALACE 1). *J Immunol Res.* 2015;2015:906349.
13. Otezla [package insert]. Summit, NJ: Celgene Corporation; 2014.
14. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet*. 2012;380:738–746.
15. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol.* 2015;73:37–49.
16. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: a phase III, randomized, controlled trial (ESTEEM 2). *Br J Dermatol.* 2015;173(6):1387–1399. Epub 2015 Nov 7.
17. Ortiz-Ibanez K, Alsina MM, Munoz-Santos C. Tofacitinib and other kinase inhibitors in the treatment of psoriasis. *Actas Dermosifiliogr.* 2013;104:304–310.
18. Ruckert R, Asadullah K, Seifert M, et al. Inhibition of keratinocyte apoptosis by IL-15: a new parameter in the pathogenesis of psoriasis? *J Immunol*. 2000;165:2240–2250.
19. Boy MG, Wang C, Wilkinson BE, et al. Double-blind, placebo-controlled, dose-escalation study to evaluate the pharmacologic effect of CP-690,550 in patients with psoriasis. *J Invest Dermatol.* 2009;129:2299–2302.
20. Dowty ME, Lin J, Ryder TF, et al. The pharmacokinetics, metabolism, and clearance mechanisms of tofacitinib, a janus kinase inhibitor, in humans. *Drug Metab Dispos.* 2014;42:759–773.
21. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol*. 2012;167:668–677.
22. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two, randomised, placebo-controlled, Phase 3 trials. *Br J Dermatol.* 2015;173:949–946.
23. Bachelez H, van de Kerkhof PCM, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet*. 2015;386:552–561.
24. Xeljanz [package insert]. New York, NY: Pfizer Labs; 2015.
25. Papp K, Pariser D, Catlin M, et al. A phase 2a randomized, double-blind, placebo-controlled, sequential dose-escalation study to evaluate the efficacy and safety of ASP015K, a novel Janus kinase inhibitor, in patients with moderate-to-severe psoriasis. *Br J Dermatol*. 2015;173:767–776.
26. Ochaion A, Bar-Yehuda S, Cohen S, et al. The anti-inflammatory target A(3) adenosine receptor is over-expressed in rheumatoid arthritis, psoriasis and Crohn's disease. *Cell Immunol.* 2009;258:115–122.
27. David M, Akerman L, Ziv M, et al. Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial. *J Eur Acad Dermatol Venereol.* 2012;26:361–367.
28. Treumer F, Zhu K, Glaser R, Mrowietz U. Dimethylfumarate is a potent inducer of apoptosis in human T cells. *J Invest Dermatol.* 2003;121:1383–1388.
29. Atwan A, Ingram JR, Abbott R, et al. Oral fumaric acid esters for psoriasis. *Cochrane Database Syst Rev.* 2015;8: Cd010497.